J. Clin. Chem. Clin. Biochem.
Vol. 23, 1985, pp. 287–292

Interference by Analgesic and Antirheumatic Drugs in 25 Common Laboratory Assays

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(Received September 26/December 10, 1984)

Summary: Twenty five different analytical procedures, commonly used in clinical laboratories, were investigated for interference by eight analgesic and antirheumatic drugs. Ten of the investigated assays showed no statistically significant interference.

Acetylsalicylic acid interfered in six assays (for glucose, uric acid, protein and cholesterol). Aminophenazone significantly decreased glucose, bilirubin and protein values, whereas caffeine affected four methods (for glucose, protein and iron).

No definite influence of phenobarbital could be detected on any assay. Glucose, uric acid and iron values were altered in the presence of diclofenac. Indomethacin interfered in glucose, urea, uric acid and protein assays.

Samples containing ibuprofen had altered creatinine, bilirubin and iron values, whereas ketoprofen interfered in glucose and iron determination.

Untersuchung von 25 üblichen Laboratoriumsmethoden hinsichtlich ihrer Störanfälligkeit durch Analgetica und Antirheumatica.

Zusammenfassung: Fünfundzwanzig verschiedene analytische, in klinischen Laboratorien übliche Verfahren wurden hinsichtlich ihrer Störanfälligkeit durch acht Analgetica und Antirheumatica untersucht. Zehn dieser Methoden zeigten keine statistisch signifikante Störung.

Acetylsalicylsäure störte bei sechs Verfahren zur Bestimmung von Glucose, Harnsäure, Protein und Cholesterin. Aminophenazon verminderte Glucose-, Bilirubin- und Proteinwerte signifikant, während Coffein vier Methoden zur Bestimmung von Glucose, Protein und Eisen störte.

Phenobarbital war ohne jeglichen Einfluß auf die untersuchten Methoden. Glucose-, Harnsäure- und Eisenwerte waren in Gegenwart von Diclofenac verändert. Indomethacin störte Glucose-, Harnstoff-, Harnsäure- und Proteinbestimmungen. Ibuprofen enthaltende Proben ergaben veränderte Kreatinin-, Bilirubin- und Eisenwerte, während Ketoprofen bei Glucose- und Eisenbestimmungen störte.

Introduction

In our previous investigation, effects of analgesic and antirheumatic drugs on the assay of serum enzymes (1) and SMA II procedures (2) were examined.

Acetylsalicylic acid, aminophenazone, indomethacin, diclofenac, ibuprofen and ketoprofen are widely used in the treatment of various rheumatic diseases. Analgetic preparations containing acetylsalicylic acid, aminophenazone, phenobarbital or caffeine are also frequently used in self-medication. It is thus important to know whether these drugs alter clinical laboratory test results.

In the present work, we investigated the effects of these eight drugs (in vitro) on 25 of the most frequently used methods for the determination of glucose, urea, uric acid, creatinine, bilirubin, protein, cholesterol, triglycerides and iron.

Tab. 1. Concentrations of added drugs in reconstituted lyophilized human sera.

Drug	Concentration (μmol/l)
Acetylsalicylic acid [2-(acetyloxy)benzoic acid]	8326
Aminophenazone (4-dimethylamino-2,3-dimethyl-l-phenyl-3 pyrazolin-5-one)	540
Caffeine (1,3,7-trimethylxanthine)	772
Phenoarbital [5-ethyl,5-phenyl-2,4,6(1H, 3H, 5H)-pyrimidinetrione]	1076
Ibuprofen [α-methyl-4-(2-methylpropyl)-benzenacetic acid]	970
Diclofenac, 2-[(2,6-dichlorophenyl)-amino]-benzenacetic acid	71
Indomethacin [1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid]	35
Ketoprofen [2-(3-benzoylphenyl)-propionic aicd]	236

Materials and Methods

To examine the drug interferences in common laboratory assays, the general protocol by *Siest* et al. (3) was followed. Commercial lyophilized human sera were reconstituted with solutions of each drug tested. The drug concentrations (tab. 1) were approximately ten times the maximal therapeutic levels (4–7).

Aqueous solutions of acetylsalicylic acid, aminophenazone, caffeine, phenobarbital, diclofenac and indomethacin were made. For control sample preparation, the drug solutions were replaced by distilled water. To dissolve ibuprofen and ketoprofen, ethanol was added in a final concentration of 200 g/l, and additional control samples were prepared, containing the same concentration of ethanol.

Glucose, urea, uric acid, creatinine, bilirubin, protein, cholesterol, triglyceride and iron concentrations were determined by various methods commonly used in clinical laboratories. The principles and reference data of the methods are shown in table 2.

For each method, six replicate tests were performed on control samples and samples containing the drug; the statistical parameters: mean value ($\bar{x}$) and standard deviation (s) were determined. Using *Student*'s t-test, the significance of the differences between values obtained in sera with and without drugs was assessed. All tests for a specific group of samples (sera containing the drug and corresponding controls) were completed in a single run.

The interferences observed were studied further using lower drug concentrations down to the therapeutic levels. Concentrations of drugs in samples were gradually decreased and drug effects tested, until statistically unsignificant differences were found.

The assays were performed with a Pye Unicam spectrophotometer SP 8-100.

Tab. 2. The methods used for the determination of analytes.

Analyte	Method	Reference
Glucose	Hexokinase and glucose-6-phosphate dehydrogenase	8
	Glucose dehydrogenase	9
	Glucose oxidase and peroxidase, using 4-aminophenazone and 2,4-dichlorphenol as chromogen	10
	Glucose oxidase and peroxidase, using ABTS as chromogen	11
	o-Toluidine	12
Urea	Urease and glutamate dehydrogenase	13
	Phenol-hypochlorite	14
	Diacetylmonoxime	15
Uric acid	Uricase and catalase	16
	Uricase, catalase and aldehyde dehydrogenase	17
	Direct UV-test with uricase	18
Creatinine	Continuous, with alkaline picrate	20
	Alkaline picrate, with deproteinization	21
	Slot	22
Bilirubin	*Jendrassik-Gróf*	23
	Dimethylsulphoxide	24
	Direct spectrophotometric method (at 461 and 551 nm)	25
Protein	Biuret reaction	26
	Direct spectrophotometric method (at 280 nm)	27
Cholesterol	Enzymatic, with cholesterol esterase and cholesterol oxidase	28
	Liebermann-Burchard reaction	29
Triglycerides	Enzymatic, using lipase, glycerol kinase, pyruvate kinase and lactate dehydrogenase	30
Iron	Bathophenanthroline disulphonate	31
	α,α'-Dipyridyl (*Ramsay*)	32

Results and Discussion

The effects of analgesic and antirheumatic drugs on 25 common laboratory assays are shown in tables 3 – 5. The concentrations of analytes and their variations obtained using different methods in samples with and without the drugs are given, as well as the corresponding p values. Ten assays showed no statistically significant interference, i.e. the determination of glucose (hexokinase method), urea (with glutamate dehydrogenase and phenol-hypochlorite method), uric acid (direct UV test and phosphotungstate method), creatinine (continuous and *Slot*'s method), bilirubin (*Jendrassik-Gróf*), cholesterol and triglycerides (enzymatic assays). No definite influence of phenobarbital could be detected on any method (tab. 4).

Acetylsalicylic acid interfered in six assays (for glucose, uric acid, protein and cholesterol determination) (tab. 3). Out of five glucose assays tested, two were affected by the drug: the glucose dehydrogenase method and the glucose oxidase-peroxidase procedure using ABTS as chromogen. Acetylsalicylic acid has been reported to have no in vitro effect on the alkaline ferricyanide, *p*-HBAH and *o*-toluidine methods (33). In sera containing the drug, apparent concentrations of uric acid (with uricase and catalase) and protein (direct spectrophotometric assay) were very significantly increased ($p < 0.01$ and $p < 0.005$, respectively). *Wirth & Thompson* (34) reported interference by acetylsalicylic acid in the *Folin-Ciocalteu* protein assay in body fluids. Lower cholesterol values were obtained using the *Liebermann-Burchard* method ($p < 0.01$), which is in agreement with findings reported by *Caraway & Kammeyer* (35).

Aminophenazone significantly decreased the results for glucose (with ABTS, $p < 0.001$), bilirubin (with dimethylsulphoxide, $p < 0.05$), and protein (biuret method, $p < 0.05$). The drug is also known to increase the results of the cholesterol determination based on reaction with ferric ions in acetic acid-sulphuric acid (33, 35).

Tab. 3. Effects of acetylsalicylic acid, aminophenazone and caffeine on some common laboratory tests (N = 6, number of the degrees of freedom $\emptyset = 2N-2 = 10$).

Analyte, method	Control without drug		Acetylsalicylic acid			Aminophenazone			Caffeine		
	$\bar{x}$	s	$\bar{x}$	s	p	$\bar{x}$	s	p	$\bar{x}$	s	p
Glucose (mmol/l)											
hexokinase	4.75	0.156	4.68	0.148	>0.4	4.62	0.150	>0.2	4.71	0.069	>0.5
glucose dehydrogenase	4.24	0.099	4.32	0.339	>0.6	4.33	0.190	>0.3	4.08	0.064	<0.02
2,4-dichlorphenol	3.69	0.245	4.10	0.155	<0.02	3.56	0.230	>0.4	3.74	0.316	>0.8
ABTS	3.93	0.078	4.03	0.037	<0.05	3.61	0.033	<0.001	4.06	0.019	<0.005
o-toluidine	5.09	0.061	5.16	0.066	>0.01	5.05	0.115	>0.4	4.95	0.173	>0.1
Urea (mmol/l)											
glutamate dehydrogenase	6.00	0.241	5.79	0.273	>0.2	6.13	0.519	>0.6	6.24	0.070	>0.05
phenol-hypochlorite	6.66	0.543	6.18	0.188	>0.05	6.59	0.467	>0.8	6.57	0.386	>0.7
diacetylmonoxime	6.60	0.155	6.83	0.560	>0.4	6.42	0.428	>0.3	6.33	0.426	>0.2
Uric acid (µmol/l)											
uricase-catalase	167	5.34	177	4.45	<0.01	161	9.57	>0.25	177	11.71	>0.05
aldehyde dehydrogenase	170	2.58	170	11.92	>0.9	176	13.62	>0.3	165	5.06	>0.05
direct UV-test	178	16.18	171	13.61	>0.4	181	10.53	>0.7	163	9.28	>0.05
phosphotungstate	214	10.41	218	4.59	>0.4	209	15.81	>0.5	207	14.64	>0.4
Creatinine (µmol/l)											
continuous	90.8	1.94	89.6	1.09	>0.25	89.8	0.49	>0.25	91.3	2.16	>0.7
with deproteinization	85.6	1.602	83.3	2.077	>0.05	84.4	1.788	>0.25	84.8	1.174	>0.3
Slot	95.7	9.16	98.2	8.57	>0.6	98.9	2.94	>0.4	95.9	7.90	>0.9
Bilirubin (µmol/l)											
Jendrassik-Gróf	29.2	1.699	28.9	0.389	>0.6	27.6	0.349	>0.05	28.7	0.802	>0.5
dimethylsulphoxide	20.1	1.542	20.6	0.446	>0.5	16.4	1.196	<0.005	19.4	1.394	>0.4
spectrophotometric	20.2	1.470	19.8	1.664	>0.6	19.0	1.829	>0.25	19.6	1.420	>0.5
Protein (g/l)											
biuret	59.5	0.969	55.6	3.313	<0.025	57.7	1.605	<0.05	59.1	1.482	>0.5
spectrophotometric	51.1	1.282	55.8	1.970	<0.005	51.5	1.482	>0.6	56.7	1.908	<0.001
Cholesterol (mmol/l)											
enzymatic	2.63	0.140	2.59	0.130	>0.6	2.71	0.175	>0.4	2.66	0.145	>0.7
Liebermann-Burchard	3.31	0.103	3.08	0.109	<0.01	3.35	0.115	>0.5	3.29	0.153	>0.8
Triglycerides (mmol/l)											
enzymatic	0.78	0.041	0.79	0.045	>0.8	0.80	0.043	>0.4	0.80	0.041	>0.5
Iron (µmol/l)											
bathophenanthroline	16.9	0.956	16.0	0.821	>0.1	16.2	0.554	>0.25	16.4	0.629	>0.3
Ramsay	20.4	1.607	19.5	0.687	>0.2	18.9	0.673	>0.05	18.4	1.001	<0.05

Caffeine affected four tests (tab. 3). Glucose values were very significantly increased (ABTS method, $p < 0.005$), as well as protein (spectrophotometric assay, $p < 0.001$). Interference by caffeine in the uric acid assay using phosphotungstate has been reported (35), but the effect was found to be significant only in the determination of uric acid in urine.

Effects of diclofenac and indomethacin are shown in table 4. In samples containing these drugs, the values for glucose (with ABTS) and uric acid values (with uricase and catalase and with aldehyde dehydrogenase) were elevated. Indomethacin affected very significantly the results of the glucose determination (with glucose dehydrogenase, $p < 0.005$), and the protein determination (biuret method, $p < 0.005$).

Creatinine (with deproteinization) and iron (*Ramsay*) values were increased in sera containing ibuprofen (tab. 5). Ketoprofen interfered in glucose (with ABTS, $p < 0.02$) and iron assays (with bathophenanthroline, $p < 0.05$ and *Ramsay* method, $p < 0.005$). No data have been previously reported on analytical interferences by diclofenac, indomethacin and ketoprofen.

The effects found were studied further using lower concentrations of drugs, down to the therapeutic levels. Interference by aminophenazone in the glucose determination (with ABTS) was still evident at 216 µmol of drug per liter ($p < 0.025$). Lower concentration of diclofenac (28 µmol/l) significantly increased the results of the same test ($p < 0.05$). Figure 1 shows the dose dependence of these two interferences. In lower concentrations, other drugs did not interfere with any assay, so the effects found are significant only in cases of drug overdosage or poisoning.

Tab. 4. Phenobarbital, diclofenac and indomethacin interference in common laboratory assays (N = 6, number of the degrees of freedom $\emptyset = 10$).

Analyte, method	Control without drug		Phenobarbital			Diclofenac			Indomethacin		
	$\bar{x}$	s	$\bar{x}$	s	p	$\bar{x}$	s	p	$\bar{x}$	s	p
Glucose (mmol/l)											
hexokinase	4.75	0.156	4.88	0.215	>0.3	4.84	0.276	>0.5	4.76	0.108	>0.9
glucose dehydrogenase	4.24	0.099	4.26	0.067	>0.6	4.16	0.139	>0.3	4.44	0.071	<0.005
2,4-dichlorphenol	3.69	0.245	3.84	0.167	>0.3	3.87	0.079	>0.1	3.71	0.232	>0.3
ABTS	3.93	0.078	4.00	0.084	>0.1	4.11	0.059	<0.005	4.05	0.073	<0.05
o-toluidine	5.09	0.061	5.00	0.086	>0.05	5.15	0.057	>0.1	5.18	0.047	<0.05
Urea (mmol/l)											
glutamate dehydrogenase	6.00	0.241	6.10	0.192	>0.4	6.24	0.128	>0.05	6.23	0.352	>0.2
phenol-hypochlorite	6.66	0.543	6.60	0.310	>0.08	6.32	0.450	>0.3	6.49	0.328	>0.5
diacetylmonoxime	6.60	0.155	6.39	0.199	>0.3	6.77	0.563	>0.5	6.29	0.169	>0.02
Uric acid (µmol/l)											
uricase-catalase	167	5.34	171	8.31	>0.3	180	8.19	<0.02	179	9.18	<0.05
aldehyde dehydrogenase	170	2.58	165	6.37	>0.1	195	9.02	<0.001	183	9.70	<0.02
direct UV-test	178	16.18	182	9.51	>0.6	176	3.30	>0.7	184	17.20	>0.5
phosphotungstate	214	10.41	217	12.10	>0.6	212	7.81	>0.8	222	17.87	>0.3
Creatinine (µmol/l)											
continuous	90.8	1.94	90.7	0.75	>0.8	89.5	2.38	>0.3	88.7	1.47	>0.05
with deproteinization	85.6	1.602	85.4	0.767	>0.8	84.1	1.376	>0.1	84.7	1.591	>0.3
Slot	95.7	9.16	95.4	8.96	>0.9	100.1	9.87	>0.4	101.2	9.08	>0.3
Bilirubin (µmol/l)											
Jendrassik-Gróf	29.2	1.699	29.9	0.609	>0.8	28.4	0.841	>0.3	29.4	0.982	>0.8
dimethylsulphoxide	20.1	1.542	20.7	1.232	>0.5	18.6	1.774	>0.1	18.8	1.554	>0.2
spectrophotometric	20.2	1.470	19.0	1.471	>0.2	20.8	0.914	>0.4	21.5	1.255	>0.1
Protein (g/l)											
biuret	59.5	0.969	57.9	2.607	>0.1	60.9	2.738	>0.25	57.8	0.568	<0.005
spectrophotometric	51.1	1.282	49.9	2.282	>0.3	51.4	2.083	>0.8	52.0	3.144	>0.05
Cholesterol (mmol/l)											
enzymatic	2.63	0.140	2.58	0.164	>0.6	2.62	0.125	>0.8	2.63	0.211	>0.9
Liebermann-Burchard	3.31	0.103	3.18	0.102	>0.25	3.32	0.175	>0.9	3.25	0.151	>0.4
Triglycerides (mmol/l)											
enzymatic	0.78	0.041	0.80	0.055	>0.5	0.79	0.039	>0.8	0.78	0.035	>0.9
Iron (µmol/l)											
bathophenanthroline	16.9	0.956	16.4	1.029	>0.5	16.4	0.835	>0.4	16.5	0.964	>0.5
Ramsay	20.4	1.607	19.2	0.964	>0.1	18.4	0.377	<0.02	21.0	1.009	>0.4

Tab. 5. Effects of ibuprofen and ketoprofen on some common laboratory tests (N = 6, number of the degrees of freedom $\emptyset = 10$).

Analyte, method	Control without drug		Ibuprofen			Ketoprofen		
	$\bar{x}$	s	$\bar{x}$	s	p	$\bar{x}$	s	p
Glucose (mmol/l)								
hexokinase	4.83	0.229	4.95	0.233	>0.4	5.02	0.081	>0.1
glucose dehydrogenase	4.36	0.112	4.21	0.150	>0.1	4.30	0.163	>0.5
2,4-dichlorphenol	4.00	0.061	4.03	0.108	>0.6	4.10	0.184	>0.25
ABTS	4.10	0.081	4.11	0.044	>0.8	4.26	0.082	<0.02
o-toluidine	5.04	0.090	5.01	0.136	>0.7	5.06	0.078	>0.7
Urea (mmol/l)								
glutamate dehydrogenase	6.13	0.278	6.05	0.324	>0.6	6.16	0.107	>0.7
phenol-hypochlorite	6.65	0.353	6.55	0.582	>0.7	6.79	0.556	>0.6
diacetylmonoxime	6.19	0.225	6.23	0.264	>0.7	6.16	0.118	>0.7
Uric acid (µmol/l)								
uricase-catalase	178	8.75	181	8.60	>0.6	174	11.96	>0.5
aldehyde dehydrogenase	172	9.50	183	6.02	>0.05	178	14.66	>0.3
direct UV-test	155	6.53	160	9.83	>0.3	159	10.29	>0.7
phosphotungstate	331	11.28	333	13.96	>0.7	346	12.92	>0.05
Creatinine (µmol/l)								
continuous	92.3	1.94	92.8	2.31	>0.7	92.9	0.57	>0.5
with deproteinization	88.3	1.357	91.0	1.010	>0.005	86.9	1.668	>0.1
Slot	104	9.42	103	8.78	>0.9	105	7.88	>0.8
Bilirubin (µmol/l)								
Jendrassik-Gróf	30.5	0.368	30.3	0.777	>0.5	30.7	0.667	>0.6
dimethylsulphoxide	18.5	2.066	19.5	1.643	>0.3	20.7	1.994	<0.05
spectrophotometric	19.4	0.768	21.3	1.274	<0.025	19.2	1.615	>0.8
Protein (g/l)								
biuret	58.2	2.469	59.2	2.256	>0.25	60.8	1.457	>0.05
spectrophotometric	50.2	2.313	50.6	1.562	>0.7	52.3	2.023	>0.1
Cholesterol (mmol/l)								
enzymatic	2.88	0.080	2.90	0.103	>0.6	2.92	0.124	>0.4
Liebermann-Burchard	3.33	0.125	3.29	0.150	>0.8	3.35	0.114	>0.8
Triglycerides (mmol/l)								
enzymatic	0.86	0.017	0.87	0.009	>0.5	0.87	0.028	>0.4
Iron (µmol/l)								
bathophenanthroline	22.3	1.332	20.0	1.170	<0.02	20.3	1.210	<0.05
Ramsay	16.6	0.838	19.6	0.361	<0.001	19.49	1.372	<0.005

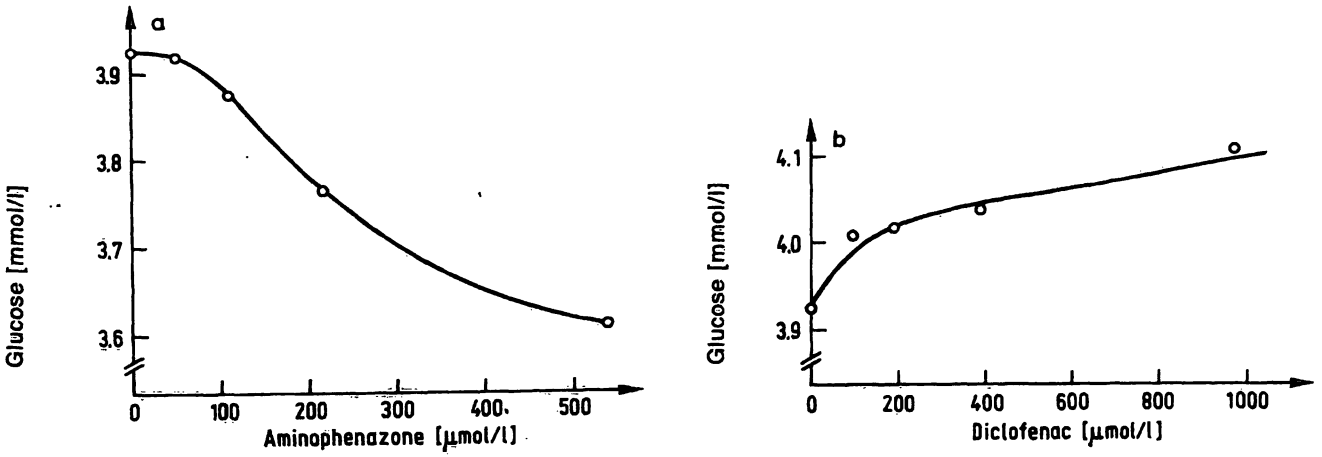

Fig. 1. Dose dependence of aminophenazone (a) and diclofenac (b) interference in the glucose assay with glucose oxidase and peroxidase using ABTS as chromogen.

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